DF/HCC Protocol #: 15-483

TITLE: A Phase 1b Study of weekly paclitaxel and oral ricolinostat for the treatment of recurrent platinum resistant ovarian, primary peritoneal, or fallopian tube cancer

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Study agents:
Ricolinostat: NSC#, supplied by Acetylon
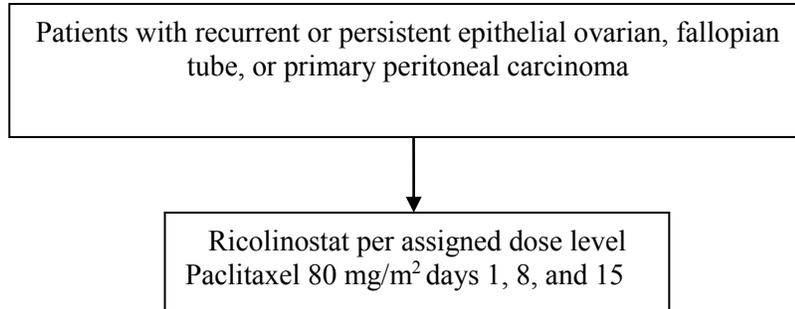Paclitaxel: Commercial
Bevacizumab: Commercial

IND #: 127956
IND Sponsor: Joyce Liu, M.D.

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SCHEMA

Patients with recurrent or persistent epithelial ovarian, fallopian tube, or primary peritoneal carcinoma

Ricolinostat per assigned dose level
Paclitaxel 80 mg/m^2 days 1, 8, and 15

Number of Participants with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter 3 participants at the next dose level.
≥ 2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional participants will be entered at the next lowest dose level if only 3 participants were treated previously at that dose.
1 out of 3	Enter at least 3 more participants at this dose level. • If 0 of these 3 participants experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional participants will be entered at the next lowest dose level if only 3 participants were treated previously at that dose.
≤ 1 out of 6 at highest dose level below the maximally administered dose	This is generally the recommended phase 2 dose. At least 6 participants must be entered at the recommended phase 2 dose.

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1. OBJECTIVES

1.1 Study Design

This is a phase Ib study of the combination of weekly paclitaxel and oral ricolinostat given to patients who have recurrent ovarian, peritoneal or fallopian tube cancer in order to establish a maximally tolerated dose (MTD). Once the MTD has been established, expansion cohorts will be performed testing (1) this combination in women with recurrent ovarian cancer and no significant neuropathy (CTCAE v4.0 grade 1 or less), (2) this combination in women with recurrent ovarian cancer and CTCAE v4.0 grade 2 neuropathy, or (3) this combination together with bevacizumab in women with recurrent ovarian cancer and no significant neuropathy.

1.2 Primary Objectives

1.2.1 To determine the MTD of oral daily ricolinostat combined with weekly paclitaxel given on a 3 out of 4 week schedule.

1.3 Secondary Objectives

1.3.1 To gain an estimate of toxicities especially peripheral neurotoxicity for combined weekly paclitaxel and ricolinostat for the treatment of recurrent ovarian, fallopian tube or peritoneal cancer.

1.3.2 To gain an estimate of preliminary response rate for these agents combined.

1.3.3 To gain an estimate of duration of response (DOR) and progression-free survival (PFS) of the combination of weekly paclitaxel and oral ricolinostat in women with recurrent ovarian cancer.

2. BACKGROUND

2.1 Ovarian Cancer

Ovarian cancer is a deadly disease that affects women globally, is diagnosed at an advanced stage in most patients and has no effective screening tests for early detection (1). The worldwide incidence of this cancer is 225,500 diagnoses per year; in the United States in 2014, 21,980 women will be diagnosed with ovarian cancer (1, 2). Global mortality of this cancer remains high with 140,200 deaths per year, and minimal improvement in mortality has been observed for women diagnosed with ovarian cancer over the past decade (1). Treatment strategies that have led to an overall survival (OS) improvement for newly diagnosed patients have included the addition of paclitaxel to platinum, the use of intraperitoneal cisplatin in patients with optimally cytoreduced cancer (<1 cm of residual cancer after upfront cytoreductive surgery), and incorporation of weekly paclitaxel versus every 3 week paclitaxel as part of upfront treatment for ovarian cancer (3-5). Neoadjuvant chemotherapy has emerged as a treatment alternative especially in patients who are unable to undergo upfront cytoreductive surgery because of the extent of cancer or those patients who are too ill or frail to undergo upfront cytoreductive surgery (6). Anti-angiogenics, specifically bevacizumab, were the first biologic to be tested in ovarian

cancer but to date addition of bevacizumab in randomized trials has demonstrated progression free survival (PFS) benefit, but no OS benefit (7-9).

In 2014, 2 agents were FDA approved for the treatment of recurrent ovarian cancer: bevacizumab in combination with chemotherapy in patients with platinum resistant ovarian cancer and the oral PARP inhibitor olaparib for women with a gBRCA mutation, recurrent ovarian cancer and who have received at least 3 lines of prior chemotherapy (FDA package insert for avastin and FDA package insert for olaparib).

Most patients will recur after being diagnosed with advanced ovarian cancer; for patients with platinum-sensitive recurrence (defined as cancer recurring ≥6 months after the last platinum), additional platinum-based therapy is given (10).   For patients with recurrent platinum resistant cancer (defined as cancer recurring <6 months after last platinum), single agent chemotherapy is administered.   New agents and rational combinations of biologics and chemotherapy are needed to improve outcomes in women with recurrent ovarian cancer.

Long-term complications of chemotherapy specifically paclitaxel include neuropathy; the most commonly used agents for ovarian cancer treatment (platinum and taxanes) lead to neuropathic complications that alter quality of life and also may lead to premature treatment discontinuation

2.2   Ricolinostat

Ricolinostat (alternative designations ACY-1215, ACY-63, ACY-161-63) is an orally active, small-molecule histone deacetylase (HDAC) inhibitor with potential for enhanced target selectivity. The chemical name of ricolinostat is 2-(Diphenylamino)-N-(7-(hydroxyamino)-7-oxoheptyl)-pyrimidine-5-carboxamide. Ricolinostat targets the Class IIb HDAC6 enzyme, which is one of 18 known histone deacetylase enzymes present in human cells. Selective inhibition of HDAC6, while retaining reduced inhibitory activity of HDAC1, 2, and 3, may uniquely enable the preservation of normal gene expression in cells while severely disrupting the ability of cells to dispose of damaged, misfolded proteins in lysosomes via the aggresome pathway, an alternative and complementary pathway to protein degradation by the proteasome complex. Because metabolically active cancer cells produce large amounts of misfolded proteins, inhibition of HDAC6 in combination other agents could result in rapid accumulation of misfolded protein, thus increasing cellular stress and potentially triggering self-destruction of diseased cells via programmed cell death that would be expected to lead to regression of disease.

Preclinical rationale exists for using histone deacetylase (HDAC) inhibition as a therapeutic strategy against ovarian cancer (12, 13). Ovarian cancer cell lines treated with HDAC inhibitors demonstrated an accumulation of cells in G1 and G2, induced apoptosis, and increased levels of acetylated histones 3 and 4. As single agents, non-selective HDAC inhibitors have little activity in recurrent ovarian cancer, however HDAC inhibitors combined with chemotherapy such as platinum agents and paclitaxel resulted in synergy (12, 13). Specifically, the combination of ricolinostat with paclitaxel enhanced tumor growth suppression in ovarian cancer xenotransplant models (Figure 1). While the precise mechanism of this synergy remains under investigation, HDAC6 controls the acetylation (and therefore activation) state of key cellular proteins with important functions in cancer, such as the chaperone HSP90 and TP53, the "safe keeper of the genome". Additionally, HDAC6 regulates acetylation of the key microtubule protein α-tubulin, whose stability is also directly impacted and implicated in the mechanism of action of paclitaxel.

Ricolinostat, via selective HDAC6 inhibition while retaining reduced and more tolerable levels of HDAC1, 2 and 3 inhibition, has the potential for a substantially reduced side-effect profile versus current HDAC inhibitor drugs and drug candidates while retaining potential for anticancer effectiveness. Ricolinostat is being studied in ongoing clinical phase 1 and 2 studies of multiple myeloma.
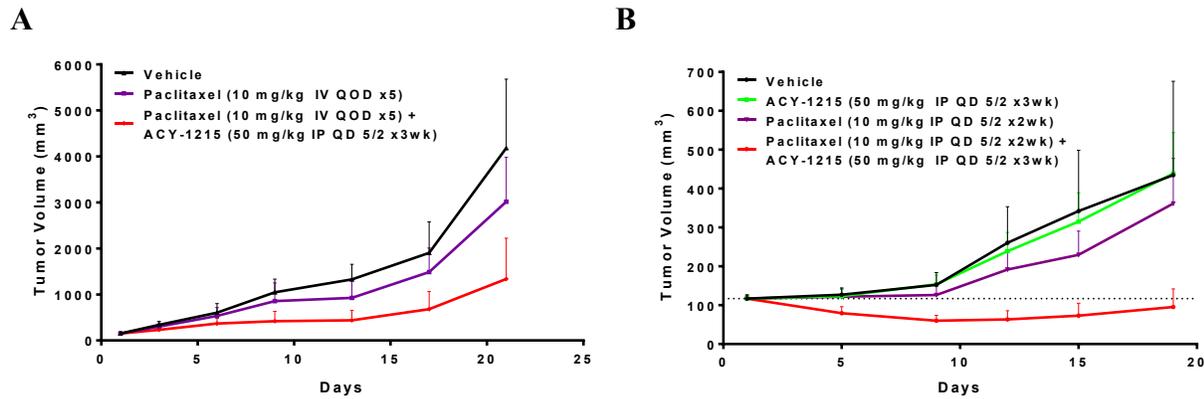

Figure 1 – Combination treatment of (A) A2780 and (B) TOV-21G ovarian cancer xenograft models with ACY-1215/ricolinostat plus paclitaxel resulted in greater suppression of tumor growth relative to control and single agent treatments.

HDAC6 inhibition is also expected to result in reversal of axonal transport defect which is observed in such diseases as Alzheimer's Disease, Huntington's Disease, ALS as well as chemotherapy-induced peripheral neuropathy caused by taxanes (paclitaxel), vinca alkaloids, and proteasome inhibitors as well as possibly platinum. In fact, treatment with ricolinostat was shown to reduce peripheral hypersensitivity in a rat model of paclitaxel-induced peripheral neuropathy (Figure 2). Thus, the rationale for combining weekly paclitaxel and ricolinostat in this study for recurrent ovarian cancer is to enhance anti-cancer activity based on the observed synergy with paclitaxel and ricolinostat in ovarian cancer cell lines and xenograft models, and to possibly mitigate the peripheral neuropathy observed with weekly paclitaxel administration.
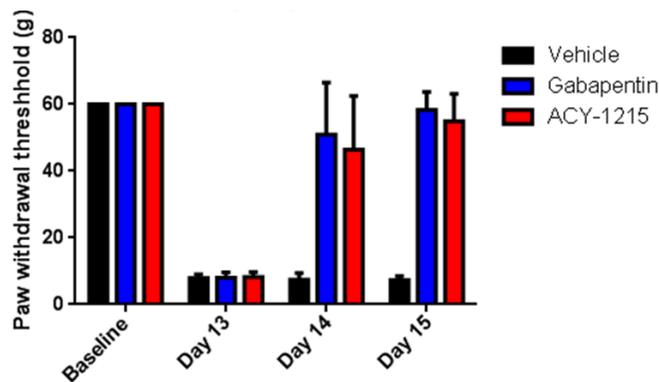

Figure 2 – ACY-1215/ricolinostat treatment reverses paclitaxel induced neuropathy in rats. Rats were treated daily with paclitaxel for 13 days (6 mg/kg on days 0-6 and 12 mg/kg on days 7-12). Confirmation of increased paw sensitivity associated with neuropathic pain was measured using the Von Frey filament test for tactile allodynia. Treatment with the analgesic Gabapentin (150 mg/kg, IP, given one hour before Von Frey test) and ACY-1215/ricolinostat (30 mg/kg, oral, twice per day) was started on day 13, and both agents led to reductions in paw sensitivity.

2.2.1   Pharmacokinetics of Ricolinostat

2.2.1.1   Nonclinical Pharmacokinetics

The absorption of ricolinostat has been extensively studied in 3 species: mouse, rat, and dog. Preclinical PK studies have been conducted predominantly under fasted conditions where ricolinostat was delivered by the oral route. In dog, fasted and fed conditions were compared for impact on exposure. Ricolinostat was rapidly absorbed (Tmax < 1 hr) following oral administration to mouse, rat and dog, with oral bioavailability of 11-19% in rodents and ~45% in dogs. Clearance following intravenous administration is less than (in mouse and dog), or equal to (in rat) hepatic blood flow. The elimination half-life (t1/2) following oral dosing is similar across all species examined (mouse, rat and dog) and generally ranges from 1 – 4 hours, with a longer t1/2 in rat at higher dose levels.

The PK of different liquid strength formulations have been compared in dogs at a dose level of 160 mg. The current liquid formulation (CLF), 20 mg/mL, attained a C_{max} of 1424 ± 324 ng/mL with an area under the plasma concentration time curve (AUC) extrapolated to infinity ($AUC_{0-\infty}$) of 4450 ± 862 ng·hr/mL compared to a C_{max} of 2070 ± 550 ng/mL and $AUC_{0-\infty}$ of 6217 ± 1236 ng·hr/mL of a diluted version of the CLF (12 mg/mL). In a separate study, the diluted version of the CLF (12 mg/mL) attained a C_{max} of 2100 ± 920 ng/mL with an $AUC_{0-\infty}$ of 8035 ± 1702 ng·h/mL compared to a C_{max} of 3440 ± 750 ng/mL and $AUC_{0-\infty}$ of 7655 ± 1893 ng·h/mL of the ALF (10 mg/mL). Subsequently, a population PK model was developed for the combined human data from the monotherapy Phase 1a trial described below with the dog data. The model adequately characterized the combined data and was used to assess the relative bioavailability of the ALF (120 mg) to the CLF. The simulation suggested a 120-mg dose of the ALF may yield a similar C_{max} and exposure to 160 mg of the CLF.

2.2.1.2   Clinical Pharmacokinetics

Clinical data are available from 123 patients with MM, of whom 15 were treated with ricolinostat monotherapy at doses up to 360 mg and 108 were treated with ricolinostat in combination with other anti-neoplastic agents in 2 clinical studies (Ricolinostat investigator's brochure). Of the 108 patients receiving combination therapy, 44 received ricolinostat in combination with bortezomib / dexamethasone, 31 received ricolinostat in combination with lenalidomide / dexamethasone, and 33 received ricolinostat in combination with pomalidomide / dexamethasone. The plasma PK of ricolinostat monotherapy in a total of 15 patients treated with ricolinostat Oral Solution, 20 mg/mL was determined in Study ACY-100 and area under the concentration curve from time 0 to 4 hours post-dose (AUC0-4) values ranged from 170±61 ng•h/mL to 1093±357 ng•h/mL at dose levels of 40 to 360 mg. Maximal plasma (Cmax) and exposure (AUC) levels observed in patients treated at 160 mg (mean Cmax 626±150 ng/mL, and mean AUC0-4 1074±439 ng•h/mL) and 240 mg (mean Cmax 719±329 ng/mL, and mean AUC0-4 1231±430 ng•h/mL) were similar, suggesting an exposure plateau was reached at dose levels ≥160 mg. The apparent elimination half-life was ~3 hours, and by 24 hours post-dose, drug levels ranged from ~1 ng/mL to below the lower limit of quantification (0.5 ng/mL). No accumulation was observed over multiple days of administration, and drug exposures at ≥160 mg were similar. The drug was rapidly absorbed (Tmax ~1 hour) from the gastrointestinal tract. Preliminary analysis of PK parameters revealed measurable levels of ricolinostat in all patients, with mean Cmax levels ranging from 85±39 to 503±195 ng/mL (0.2 to 1.2 μM).

PK results from patients treated with ricolinostat monotherapy suggest an exposure plateau was reached at dose levels ≥160 mg because PK data from 160 mg and 240 mg were similar; therefore, QD doses of ricolinostat >240 mg will not be investigated. PK data also show ricolinostat to be rapidly absorbed (Tmax ~1 hour) from the gastrointestinal tract. The apparent elimination half-life was ~3 hours, with drug levels ranging from ~1 ng/mL to below the lower limit of quantification (0.5 ng/mL) by 24 hours post-dose.

2.2.2   Pharmacodynamics

Pharmacodynamic analyses in PBMCs collected from patients receiving ricolinostat monotherapy confirm the mechanism of action of ricolinostat, with demonstration of acetylation of tubulin (an HDAC6 effect), preferentially to histone acetylation (a Class 1 HDAC effect), at clinically achievable exposures of ricolinostat (see Section 4.3.1.1).

2.2.3   Safety and Toxicities of ricolinostat in animals

Ricolinostat is a selective (10-fold) and potent inhibitor (biochemical IC50 5.7 nM) of HDAC6 over Class I HDACs 1, 2 and 3. The principal side effects associated with Class 1 HDAC inhibition in the clinic, including thrombocytopenia, neutropenia, significant gastrointestinal effects, and fatigue, have not been observed with ricolinostat in preclinical studies, most notably in the GLP 28-Day repeat-dose study in dog where the highest maximal plasma levels of ricolinostat at ≥10 μM were attained.

Cardiovascular Findings
The cardiovascular effects of ricolinostat in the dog included increased heart rate (by 19 – 24 bpm) and decreased systolic pressure (by 5 – 15 mmHg), were moderate and transient and occurred in all dose groups, including the low dose group (10 mg/kg), where maximal plasma levels were similar to the upper range of the efficacious concentration observed in preclinical studies.   One dog in the high dose group (60 mg/kg) in the cardiovascular safety study exhibited QTc prolongation several hours after maximal plasma levels were observed. These effects were not observed in the low and mid dose groups (10 and 30 mg/kg). Based on the Cmax level in this one dog versus other unaffected dogs, QTc prolongation is unlikely if the substantially lower efficacious concentration range observed in cellular and animal studies is similar in humans. Serial ECGs were performed in patients treated with ricolinostat monotherapy, with no clinically important effect of ricolinostat on ECG parameters in the course of the study.

Hematology: Red Blood Cells
Minimal to mild decrease in RBC mass was observed at all 3 ricolinostat dose levels in dog, including the low dose group (30 mg/kg/day) in the pivotal 28-day repeat dose study, with exposure and Cmax levels (Day 28) ranging from 16,800 to 26,800 ng·h/mL and 4,080 to 9,490 (9.4 to 22 μM). These levels of ricolinostat range from 2 to 4-fold higher than the upper range of the efficacious concentration observed in preclinical studies. These changes were accompanied by marginal and non-adverse increases in total protein and albumin levels. In the rat (males only), a slight reduction that was within normal limits of variability was observed in RBC parameters at ≥60 mg/kg/day.

In clinical studies of ricolinostat, hematological and clinical chemistry parameters are monitored frequently throughout each treatment cycle, as described in the protocol. Anemia has been

reported in patients treated with ricolinostat alone or in combination, and has been considered study drug-related in some cases.

Body Weight

Slight body weight decrease was observed at all 3 dose levels in the dog, including the low dose group (30 mg/kg/day) in the pivotal 28-day repeat dose study with exposure and Cmax levels (Day 28) ranging from 16,800 to 26,800 ng·h/mL and 4,080 to 9,490 (9.4 to 22 μM). These levels of ricolinostat range from 2 to 4-fold higher than the upper range of the efficacious concentration observed in preclinical studies. Body weight is measured once per treatment cycle as described in the clinical protocol. No clinically significant effect on body weight has been seen in clinical studies of ricolinostat alone or in combination.

2.2.4   Human studies of ricolinostat

Safety

Review of safety data from patients treated with ricolinostat monotherapy or in combination with bortezomib / dexamethasone or lenalidomide /dexamethasone has shown ricolinostat to be generally well tolerated and to have a manageable safety profile.

Ricolinostat Monotherapy

Among patients treated with ricolinostat monotherapy, no deaths or other SAEs were considered by the Investigator to be related to ricolinostat, and no AEs reported were considered to represent DLTs (IB). As no DLTs occurred with ricolinostat monotherapy, an MTD was not identified.

A total of 15 patients were treated with ricolinostat monotherapy at doses ranging from 40 to 360 mg. Across dose cohorts, the median duration of therapy ranged from 1.7 weeks to 12.3 weeks, with a maximum duration of therapy of 29.5 weeks.   Most (14 of 15 patients; 93%) patients treated with ricolinostat monotherapy experienced at least 1 AE. Most AEs reported were considered by the Investigator to be mild or moderate (Grade 1 or 2) in intensity and unrelated to study drug.   Among all 15 patients treated with ricolinostat monotherapy, the most common AEs, regardless of dose, were blood creatinine increased (5 patients; 33%), fatigue, hypercalcemia, and upper respiratory tract infection (4 patients each; 27%), and anemia, cough, diarrhea, and dizziness (3 patients each; 20%). Diarrhea occurred only at ricolinostat doses ≥160 mg. AEs that were assessed by the Investigator as Grade 3 or 4 intensity and possibly related to study drug were seen at ricolinostat doses ≥160 mg and were all hematologic abnormalities, including anemia (160 mg) and neutropenia and leukopenia (360 mg). None of these events was a dose-limiting toxicity (DLT), based on the protocol definitions.

2.2.5   Rationale for the dose and schedule of ricolinostat

Clinical data show that the plasma exposure of ACY-1215 CLF plateaus at levels ≥ a 160-mg dose. For this study, a 120-mg dose of the alternative liquid formulation (ALF) of 10 mg/mL ACY-1215 is predicted to yield exposure similar to that obtained with a 160-mg dose of ACY-1215 CLF based on population PK modeling of human and dog PK data (see Section 2.2.1.1). Doses will be escalated to determine if an MTD exists for ACY-1215 when administered in an ALF in combination with paclitaxel.

2.3   Paclitaxel

Weekly paclitaxel is an established standard of care therapy for recurrent ovarian cancer and several studies have demonstrated activity of weekly paclitaxel for the treatment of recurrent ovarian cancer.

In addition, peripheral neuropathy that persists post-initial platinum and taxane-based chemotherapy makes re-treatment with additional taxanes and platinum more challenging. Table 1 summarizes the results of weekly paclitaxel in recurrent ovarian cancer.

Table 1:   Summary of Response Rates to Weekly Paclitaxel Based on Published Literature

Study-Reference	N	Population	Regimen	Response	Survival
14	53	Taxane- and platinum-resistant	80 mg/m2 weekly	25% total (3% CR, 22% PR)	24 wk PFS 58 wk OS
15	57	Platinum-resistant	80mg/m2 weekly	56% total (12% CR, 44% PR)	5.0 mo PFS 13.7 mo OS
16	208 (randomized – 105 pts with weekly paclitaxel)	≤ 1 prior platinum-containing regimen	67 mg/m2 weekly	35% total (12% CR, 23% PR)	6.1 mo PFS 13.6 mo OS
17	22	Retrospective Taxane- and platinum-resistant	60-80 mg/m2 weekly	50% (27% CR, 23% PR)	27 wk PFS (in responders)
18	28	Mostly taxane and platinum resistant	80mg/m2 for 6-8 weeks	50% total (50% PR)	6 mo PFS (in SD or responders)
19	39	1-3 prior platinum-containing regimens	80m/gm2 3 wk on/1 wk off	45.9% (13.5% CR, 32.4% PR)	
20	32	Taxane and platinum-resistant	80mg/m2 6 wks on / 2 wks off	31.2% (3.1% CR, 28.1% PR)	
21	48	Platinum-resistant (6 mo)	80mg/m2 weekly - cont x 12 weeks - optional 3 wk on/1 wk off p 12 wks	20.9% total (4.2% CR, 16.7% PR)	3.6 mo "response duration" Survival data not reported
22	34	Platinum-	80 mg/m2	53% total	6.10 mo

		resistant	weekly	(9% CR, 44% PR)	PFS 10.43 mo OS
23	49	Retrospective	Different doses	28% total	149 d PFS 359 d OS
24	53	Retrospective No taxane in prior 6 months	80-90 mg/m2 weekly	48% total (4% CR, 43% PR)	4.8 mo PFS 13.5 mo OS
25	70 (29 weekly paclitaxel vs. 41 paclitaxel/ bevacizumab)	Retrospective	60-70mg/m2 weekly	48% total (17% CR, 31% PR)	6.2 mo PFS 18.8 mo OS

2.4   Rationale

The rationale for this study is as follows:
1) Weekly paclitaxel is a standard of care treatment for women with recurrent ovarian, peritoneal or fallopian tube cancer. Despite evidence of activity in recurrent ovarian cancer, resistance eventually develops to paclitaxel. Additionally, the development of peripheral neurotoxicity may limit paclitaxel administration even when it remains an active agent.

2) Ricolinostat is an HDAC6 inhibitor that shows pre-clinical synergy when combined with weekly paclitaxel in ovarian cancer PDX models.

3) In addition, ricolinostat, because it is an HDAC6 inhibitor, may have additional benefits in an ovarian cancer population because of its ability to restore impaired axonal transport and may lessen observed neurotoxicity with weekly paclitaxel.

3. PARTICIPANT SELECTION

3.1   Eligibility Criteria

3.1.1   Participants must have recurrent or persistent epithelial ovarian, fallopian tube or primary peritoneal carcinoma. Histologic documentation of the original primary tumor is required via the pathology report.

3.1.2   Participants must have measurable disease by RECIST 1.1 criteria. See Section 11 for the evaluation of measurable disease.

3.1.3   Participants must have had at least one prior platinum-based chemotherapeutic regimen for management of primary disease (e.g., a regimen containing carboplatin, cisplatin, or another organoplatinum compound). This initial treatment may have included intraperitoneal therapy, consolidation, biologic/targeted (non-cytotoxic) agents (e.g., bevacizumab) or extended therapy administered after surgical or non-surgical assessment.

Participants are allowed to receive, but are not required to receive, biologic/targeted (non-cytotoxic) therapy as part of their primary treatment regimen.

3.1.4   Participants must have recurrence within 12 months of their last platinum-containing regimen.

3.1.5   Age 18 years or older

3.1.6   ECOG performance status 0 or 1

3.1.7   Life expectancy of greater than 16 weeks

3.1.8   Participants must have normal organ and marrow function as defined below:

- leukocytes   ≥3,000/mcL
- absolute neutrophil count   ≥1,500/mcL
- platelets   ≥100,000/mcL
- total bilirubin   ≤ the institutional upper limit of normal
- AST(SGOT)/ALT(SGPT)   ≤2.5 × institutional upper limit of normal
- creatinine   within normal institutional limits
                                         OR
- creatinine clearance   ≥60 mL/min/1.73 m^2 for participants with creatinine levels above institutional normal.

3.1.9   Previous toxicities from previous treatment must have resolved to grade 1 or less
        3.1.9.1   For patients in expansion cohort B, stable Grade 2 neuropathy will be allowed.

3.1.10 The effects of both paclitaxel and oral ricolinostat on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

3.1.11 Participants must be able and willing to swallow pills and to absorb oral medications.

3.1.12 Ability to understand and the willingness to sign a written informed consent document

3.1.13 Participants must be able and willing to follow protocol instructions and schedules.

3.2   Exclusion Criteria

3.2.1   Participants who have had chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier. In addition, no small molecule kinase inhibitors or any other type of investigational agent may have been administered within 4 weeks before first dose of study treatment.

3.2.2   Participants may not be receiving any other investigational agents for treatment of their cancer.

3.2.3   No hormonal therapy is allowed within 1 week of initiating study treatment.

3.2.4   Participants may not have had radiation to >25% of the bone marrow.

3.2.5   Prior treatment with a histone deacetylase inhibitor.

3.2.6   Participants may have received prior treatment with weekly paclitaxel; however, participants who have had progression on or within 8 weeks of their last dose of weekly paclitaxel will not be eligible.

3.2.7   Participants with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

3.2.8   History of severe allergic reactions attributed to compounds of similar chemical or biologic composition to either paclitaxel or ricolinostat. Patients who require administration of paclitaxel through a desensitization procedure are not eligible for this study.

3.2.9   Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.10 Patients with chronic viral illnesses such as HIV-positivity and active hepatitis B or C are ineligible because they are at increased risk of lethal infections when treated with marrow-suppressive therapy.

3.2.11 Any signs, symptoms, and/or radiographic evidence of a complete or partial bowel obstruction

3.2.12 Patients with a history of other invasive malignancies, with the exception of non-melanoma skin cancer and other specific malignancies as noted below, are excluded if there is any evidence of other malignancy being present within the last three years. Patients are also excluded if their previous cancer treatment contraindicates this protocol therapy.
- Carcinoma in situ of the breast or cervix
- Primary endometrial cancer meeting the following conditions: Stage not greater than

IA, grade 1 or 2, no more than superficial myometrial invasion, without vascular or lymphatic invasion; no poorly differentiated subtypes, including papillary serous, clear cell, or other FIGO grade 3 lesions.

3.2.13 Patients who have received prior chemotherapy for any abdominal or pelvic tumor OTHER THAN for the treatment of ovarian, fallopian tube, or primary peritoneal cancer within the last three years are excluded. Patients may have received prior adjuvant chemotherapy for localized breast cancer, provided that it was completed more than three years prior to registration, and the patient remains free of recurrent or metastatic disease.

3.2.14 Patients with clinically significant cardiovascular disease. This includes:
- Myocardial infarction or unstable angina within 6 months prior to registration.
- New York Heart Association (NYHA) Class II or greater congestive heart failure. (see Appendix III)
- History of serious ventricular arrhythmia (i.e., ventricular tachycardia or ventricular fibrillation) or serious cardiac arrhythmia requiring medication. This does not include asymptomatic atrial fibrillation with controlled ventricular rate.
- Any history of congenital long QT syndrome
- The subject has a corrected QT interval calculated by the Fridericia formula (QTcF) >500 ms within 28 days before randomization. Note: if initial QTcF is found to be > 500 ms, two additional EKGs separated by at least 3 minutes should be performed. If the average of these three consecutive results for QTcF is ≤500 ms, the subject meets eligibility in this regard.

3.2.15 Patients with serious non-healing wound, ulcer, or bone fracture within 28 days before registration. Patients should not have had any major surgical procedures within 28 days of registration.

3.2.16 Patients with history of organ transplant.

3.2.17 Patients with active bleeding or pathologic conditions that carry high risk of bleeding, such as known bleeding disorder, coagulopathy, or tumor involving (in contact with, invading or encasing) major vessels.

3.2.18 Gastrointestinal disorders that may interfere with absorption of oral agents, such as malabsorption syndromes. Additionally, patients requiring drainage gastrostomy (e.g. PEG tube) and/or parenteral hydration and/or nutrition support are not eligible

3.2.19 Patients with history or evidence upon physical examination of CNS disease, including primary brain tumor, seizures which are not controlled with non-enzyme inducing anticonvulsants, any brain metastases and/or epidural disease, or history of cerebrovascular accident (CVA, stroke), transient ischemic attack (TIA) or subarachnoid hemorrhage within six months prior to the first date of study treatment.

3.2.20 The following are additional exclusion criteria for patients enrolling in Expansion Cohort C:

    3.2.20.1   Uncontrolled blood pressure (>140/90). Patients should have a blood pressure of ≤140/90 taken by a medical professional within one week of starting on study

    3.2.20.2   Proteinuria >2+ on urinalysis

    3.2.20.3   Serosal involvement of the bowel that would render the patient at increased risk of gastrointestinal perforation

    3.2.20.4   Other gastrointestinal orders that could increase the potential risk of perforation or fistula formation, including but not limited to the following:

- Intra-abdominal metastases/tumor invading the GI mucosa
- Active peptic ulcer disease within 28 days of registration
- Inflammatory bowel disease (including ulcerative colitis and Crohn's disease), diverticulitis, cholecystitis, symptomatic cholangitis, or appendicitis.

    3.2.20.5   Any of the following within 6 months of registration:

- abdominal fistula
- gastrointestinal perforation
- bowel obstruction or gastric outlet obstruction
  Note: patients requiring drainage gastrostomy (e.g., PEG tube) and/or parenteral hydration and/or nutrition are not eligible
- intraabdominal abscess
  Note: complete resolution of an intraabdominal abscess must be confirmed prior to registration even if the abscess occurred more than 6 months prior to registration.

    3.2.20.6   Major surgery within 3 months of the first dose of study drugs if there were no wound healing complications or within 6 months of the first dose of study drugs if there were wound complications.

3.2.21 Any serious and/or unstable pre-existing medical disorder (aside from malignancy exception above), psychiatric disorder, or other conditions that could interfere with subject's safety, obtaining informed consent or compliance to the study procedures, in the opinion of the Investigator.

3.3   Inclusion of Women and Minorities

Women of all races and ethnic groups are eligible for this trial.

4. REGISTRATION PROCEDURES

4.1   General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

4.2   Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

4.3   General Guidelines for Other Investigative Sites

N/A

4.4   Registration Process for Other Investigative Sites

N/A

5.   TREATMENT PLAN

5.1   Treatment Regimen

All patients will receive ricolinostat administered in the 10mg/mL ALF daily on days 1-21 of each treatment cycle, with the exception of dose level -1, where ricolinostat is given on days 1-5, 8-12 and 15-19 of a 28-day cycle. On paclitaxel administration days, paclitaxel is to be given immediately after ricolinostat. Study Day 1 is defined as the first day the patient receives study drug. Following completion of the first cycle, patients may continue the study at their assigned dose of ricolinostat.

Weekly paclitaxel will be administered weekly on days 1, 8, and 15 of a 28 day cycle, with 28 consecutive days defined as a treatment cycle. Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

Dose Level	Ricolinostat (mg) (oral administration in a 28-day cycle)	Paclitaxel (mg/m2) (days 1, 8, and 15 of a 28-day cycle) (IV administration)
Level -1	80 mg daily 5 days per week out of 7	80
Level 1 (starting dose)	80 mg daily days 1-21	80
Level 2	120 mg daily days 1-21	80

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| Level 3 | 180 mg daily days 1-21 | 80 |
| Level 4 | 240 mg daily days 1-21 | 80 |

Additional dose levels may be added based upon toxicities observed within dose levels. In addition, 3 additional patients may be placed on a dose level once the MTD has been established in order to obtain additional information about the toxicities of that dose level.

After a recommended Phase 2 dosing (RP2D) has been determined, three 10-patient expansion cohorts will be enrolled at this dosing level to gain greater experience with this drug combination, to explore the potential effects of combining ricolinostat with paclitaxel on the development of chemotherapy-induced peripheral neuropathy (cohort A: PN grades 0 and 1, cohort B: PN grade 2), and to explore the safety of the RP2D dosing in combination with bevacizumab given FDA approval of paclitaxel and bevacizumab for recurrent platinum-resistant ovarian cancer . Dosing within these three expansion cohorts would be as follows:

- Expansion cohort A:
  - Paclitaxel 80mg/m^2 weekly days 1, 8, and 15 of a 28-day cycle
  - Ricolinostat dosing as identified as the RP2D combination dose
- Expansion cohort B:
  - Paclitaxel 70mg/m^2 weekly days 1, 8, and 15 of a 28-day cycle
  - Ricolinostat dosing as identified as the RP2D combination dose
- Expansion cohort C:
  - Paclitaxel 80mg/m^2 weekly days 1, 8, and 15 of a 28-day cycle
  - Bevacizumab 10mg/kg days 1 and 15 of a 28-day cycle
  - Ricolinostat dosing as identified as the RP2D combination dose

5.2   Pre-Treatment Criteria

5.2.1   Screening Visit

Participants must meet criteria at screening as outlined in section 3.0. All screening tests must be done within 4 weeks of study entry with exception of tumor measurements which must be done within 2 weeks of starting treatment.

5.2.2   Hematologic Criteria

Cycle 1, Day 1:
- Absolute neutrophil count $\geq$ 1500/mcL
- Platelets $\geq$ 100,000/mcL

Cycles 2 and beyond, Day 1
- Absolute neutrophil count $\geq$ 1000/mcL
- Platelets $\geq$ 100,000/mcL

5.2.3   All Cycles, Day 1

Participants must have the following:

- Serum creatinine ≤ 1.5x institutional upper limit of normal (ULN) or calculated creatinine clearance of ≥ 50 mL/min.
- AST/ALT ≤ 3 times ULN or ≤ 5 times ULN if liver metastases are present.
- ECOG performance status of 0 or 1.
- No evidence of life-threatening medical problems.
- No evidence of a bowel obstruction or an impending bowel obstruction.
- Continued willingness and ability to swallow pills and absorb oral medications.
- For Expansion Cohort C patients:
  - Blood pressure ≤140/90 on days receiving bevacizumab.
  - Urine protein of 2+ or less by urinalysis

5.2.4   For Cycles 2 and Beyond

All treatment-related toxicities experienced during the preceding cycle (excepting alopecia) must have returned to grade 1 or less

5.3   Agent Administration

5.3.1   Ricolinostat/ACY-1215

ACY-1215 Oral Solution 10 mg/mL will be supplied by Acetylon Pharmaceuticals, Inc. as a liquid for oral administration in amber glass bottles and will be stored in the pharmacy at -20ºC. Additional storage conditions and dose preparation instructions will be provided in detail within the Pharmacy Manual. Study center pharmacy personnel will prepare individual patient doses of ACY-1215 Oral Solution 10 mg/mL to be administered either during scheduled study-center visits or by the patient at home.

Administration: Ricolinostat will be administered PO QD at least 1 hour after ingestion of food and followed by 4oz of water. Patients will be instructed not to ingest food or other PO medication for at least 2 hours after each ricolinostat dose. On other study drug administration days that coincide with scheduled study-center visits, ricolinostat may be administered at the study center or at home. Dosing weight will be per institutional standard.

Dosing: Ricolinostat dosing will be escalated as per the dosing level table in Section 5.1 Dosing for individual participants will be determined by their enrollment cohort.

Hydration: No prehydration is required. Prehydration may be administered per clinical practice based on clinical factors individual to the participant.

Order of Administration: Participants should take ricolinostat orally immediately (within 30 minutes) of initiating paclitaxel infusion on paclitaxel administration days.

Adverse Effects: Observed side effects with ricolinostat are described in Section 7.1.1. Investigators should also refer to the Investigator's Brochure for additional details and information.

5.3.2   Paclitaxel

Administration: Administration of paclitaxel should be prepared and administered per institutional standards, and as per the FDA package insert.

Dosing: The starting dose of paclitaxel will be 80mg/m2 weekly on days 1, 8, and 15 of a 28-day cycle. Dose modifications should be as described in Section 6.

Paclitaxel must be diluted prior to infusion. Paclitaxel will be diluted in 0.9% Sodium Chloride for Injection, USP; 5% Dextrose Injection, USP; 5% Dextrose and 0.9% Sodium Chloride Injection, USP; or 5% Dextrose in Ringer's Injection to a final concentration of 0.3 to 1.2mg/mL. The solutions are physically and chemically stable for up to 27 hours at ambient temperature (approximately 25°C / 77°F) and room lighting conditions.

Drug, Tubing and Filtration: Paclitaxel should be administered through an inline filter with a microporous membrane not greater than 0.22 microns. Use of filter devices such as IVEX-2® or IVEX-HP®, which incorporate short inlet and outlet PVC-coated tubing has not resulted in significant leaching of DEHP.

NOTE: In order to minimize patient exposure to the plasticizer DEHP, which may be leached from PVC infusion bags or sets, diluted paclitaxel solutions should be stored in bottles (glass, polypropylene) or plastic (polypropylene, polyolefin) bags and administered through polyethylene-lined administration sets.

Hydration: No prehydration is required. Prehydration may be administered per clinical practice based on clinical factors individual to the participant.

Premedications: All patients should be premedicated with corticosteroids, diphenhydramine, and H2 antagonists prior to paclitaxel administration in order to prevent severe hypersensitivity reactions.

Order of Administration: Participants should take ricolinostat orally immediately (within 30 minutes) of initiating paclitaxel infusion on paclitaxel administration days.

Adverse Effects: Consult the package insert for the most current and complete information.

5.4   Definition of Dose-Limiting Toxicity (DLT)

Management and dose modifications associated with the above adverse events are outlined in Section 6.

The definition of a DLT-evaluable patient includes the following:
1) The patient is not removed from the study during cycle 1 because of disease progression or withdrawal of consent
2) The patient received weekly paclitaxel as per the protocol
3) The patient demonstrated proof via the pill diary that all doses of ricolinostat were taken or attempted to be taken, and

4) The patient was compliant with all study procedures and laboratory measurements.

The definition of a DLT is defined by the following criteria and will be assessed during cycle 1 only:

1) Any treatment-related CTCAE v4.0 grade 3 or 4 non-hematologic event with the following exceptions:
   a. Grade 3/4 nausea, vomiting or diarrhea, unless grade 3/4 symptoms persist without resolution despite optimal symptomatic treatment
   b. Grade 3 transaminitis present for ≤ 7 days
   c. Easily correctable asymptomatic Grade 3 laboratory abnormalities
2) Any of the following treatment-related hematologic events:
   a. Febrile neutropenia defined as Grade 3/4 neutropenia with fever $\geq 38.5°C$ and/or demonstrated infection
   b. Any Grade 4 neutropenia last 5 days or more
   c. Any incident of Grade 4 thrombocytopenia (platelet count $< 25,000/\mu L$)
   d. Failure of the absolute neutrophil count (ANC) to recover to $\geq 1000/\mu L$ or platelets to recover to $\geq 50,000/\mu L$ within 14 days of therapy, and
   e. Any incident of Grade 4 anemia
3) Any clinically significant treatment-related abnormal laboratory value resulting in a dose delay of >14 days and/or
4) <75% of ricolinostat dosing taken by the patient during the first cycle due to any study-related toxicity

Dose escalation will proceed within each cohort according to the following scheme. Dose-limiting toxicity (DLT) is defined above. Patients who are not evaluable for DLT will be replaced.

Number of Participants with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter 3 participants at the next dose level.
≥ 2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional participants will be entered at the next lowest dose level if only 3 participants were treated previously at that dose.
1 out of 3	Enter at least 3 more participants at this dose level. • If 0 of these 3 participants experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional participants will be entered at the next lowest dose level if only 3 participants were treated previously at that dose.
≤ 1 out of 6 at highest dose level below the maximally administered dose	This is generally the recommended phase 2 dose. At least 6 participants must be entered at the recommended phase 2 dose.

5.5   General Concomitant Medication and Supportive Care Guidelines

The Overall PI should be alerted if the participant is taking any agent known to be a strong inhibitor or inducer of CYP3A4 or CYP2C8. A reference to interactors with CYP450 enzymes may be found at http://medicine.iupui.edu/clinpharm/ddis/.

Participants on chronic medications that can be given concomitantly with protocol drugs should be maintained on the same dose and dose schedule throughout the study period, as medically feasible. The investigator should instruct the participant to notify the study site about any new medications he/she takes after the start of the study drug.

All supportive measures consistent with optimal patient care will be given throughout the study. Bisphosphonates, vitamin D and calcium supplementation, topical medications, antiemetics, anti-diarrheal medications, anticoagulants and anti-infective agents may be used at the discretion of the treating physician.

In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient is permitted with the following exceptions:

- Other investigational therapies must not be used while the participant is on the study.

- Myeloid growth factors are not permitted during the first cycle of therapy but may be used during the subsequent cycles as determined by the treating physican in order to maintain the patient on study and following standard of care guidelines.

- Anticancer therapy (chemotherapy, biologic or radiation therapy, and surgery) other than the study treatments must not be given to participants while he/she is on the study. If such agents are required for a participant then the participant must be removed from this study.

- Herbal preparations/medications are not allowed throughout the study. These herbal medications include, but are not limited to: St. John's Wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days prior to first dose of study drug. Fruits include the CYP3A inhibitors Seville oranges, grapefruit, pummelos, or exotic citrus fruits.

5.6   Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment may continue for indefinitely or until one of the following criteria applies:

- Disease progression

- Intercurrent illness that prevents further administration of treatment

- Unacceptable adverse event(s)

- Participant demonstrates an inability or unwillingness to comply with the treatment regimen and/or documentation requirements

- Participant decides to withdraw from the protocol therapy

- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

An ODQ Treatment Ended/Off Study Form will be filled out when a participant is removed from protocol therapy. This form can be found on the ODQ website or obtained from the ODQ registration staff.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI:

Joyce Liu, M.D.
Dana-Farber Cancer Institute
450 Brookline Ave.
Boston, MA 02215
Phone: (617) 632-5269 or pager: (617) 632-3352

5.7 Duration of Follow Up

Participants will be followed for 30 days after removal from protocol therapy or until death, whichever occurs first. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.8 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:
- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF).

A ODQ Treatment Ended/Off Study Form will be filled out when a participant comes off study. This form can be found on the ODQ website or obtained from the ODQ registration staff.

6. DOSING DELAYS/DOSE MODIFICATIONS

6.1 Dose Modification Tables

Dose delays and modifications will be made as indicated in the following table(s). The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. **No dose modifications are allowed in cycle 1** (except in the setting of a DLT being declared; in this setting, dose modification may be considered after discussion with the PI for the patient developing the DLT if continued study treatment is being considered). No dose increases will be allowed after a dose reduction.

Paclitaxel dose reductions will be per the following table:

Drug	Starting Dose	Dose Reduction Level A	Dose Reduction Level B
Paclitaxel	80 mg/m^2/week	70 mg/m^2/week	60 mg/m^2/week

Ricolinostat dose reductions should be made per the dose levels outlined below. Patients must start dose reductions from the dose level assigned at study entry. Intrapatient dose escalations are not allowed. Patients on dose levels that are higher than the MTD (once an MTD has been identified) may have their dosing decreased to the MTD at the discretion of the treating investigator, in discussion with the overall PI.

Dose Level	Ricolinostat (mg) (oral administration in a 28-day cycle)	1st dose reduction	2nd dose reduction
Level -1	80 mg daily 5 days per week out of 7	Off therapy	N/A
Level 1 (starting dose)	80 mg daily days 1-21	80 mg daily 5 days per week out of 7	Off therapy
Level 2	120 mg daily days 1-21	80 mg daily days 1-21	80 mg daily 5 days per week out of 7
Level 3	180 mg daily days 1-21	120 mg daily days 1-21	80 mg daily days 1-21
Level 4	240 mg daily days 1-21	180 mg daily days 1-21	120 mg daily days 1-21

Any dose modifications should be carried through to future cycles of therapy once performed.

6.2 General Management of Adverse Events

Patients should be assessed clinically for toxicity at each clinic visit through use of the NCI CTCAE version 4 grading scale. Dosing should occur only if a patient's clinical assessment and laboratory test values are acceptable.

Dose modifications for specific toxicities are outlined in the sections below. In general, patients

who experience any treatment-related grade 3 or higher non-hematologic toxicities or grade 2 non-hematologic toxicities that persist despite maximal support (excluding those outlined below and any easily correctable asymptomatic grade 3 laboratory abnormalities) should have study treatment held until these symptoms resolved to grade 1 or less. Treatment may then be resumed with dose reductions as per Section 6.1. The investigator may choose to reduce the dose of paclitaxel, ricolinostat, or both, depending on which drugs are felt to be contributory to the development of the specific adverse event. Patients whose toxicities do not recover to grade 1 or less within 14 days should be removed from protocol-directed therapy. No dose modifications are allowed for alopecia.

Patients who require treatment delays for non-treatment-related toxicities should be discussed with the PI.

6.3   Hematologic Toxicities

Study treatment should not be administered unless the patient meets hematologic parameters of ANC ≥ 1000/mm^3 and platelet count ≥ 100,000/mm^3 on day 1 of the cycle or ANC ≥ 1000/mm^3 and platelet count ≥ 75,000/mm^3 on days 8 and 15 of the cycle (Of note, on Cycle 1 Day 1, patients must have an ANC ≥ 1500/mm^3, as per Section 5.1.2. Treatment may be delayed for a maximum of 14 days until these parameters are met. If patient counts fail to recover adequately within 14 days, protocol-directed therapy should be discontinued.

Dose modifications should occur for neutropenic or thrombocytopenic events, as detailed in the following tables, once the patient's ANC and/or platelet counts have recovered to meet the hematologic parameters for dosing outlined above. Dose modifications should be carried through to future cycles of therapy once performed.

Table 6.3.A: Dose modifications for neutropenia		
	Hematologic Event	Dose Modification
Initial Occurrence	Febrile neutropenia[†] Grade 4 neutropenia lasting ≥ 7 days ANC < 1000/mcL on Day 1, 8, or 15 Treatment delay > 7 days for neutropenia	Reduce paclitaxel by one dose level Initiate G-CSF if not already receiving
Second Occurrence	If any of the above toxicities occur after initial dose reduction	Reduce paclitaxel by one dose level[†] Reduce ricolinostat by one dose level
Third occurrence	If any of the above toxicities occur after two dose reductions	Discontinue patient from protocol-directed therapy
[†]Paclitaxel may not be reduced below 60mg/m^2 weekly. If neutropenic event occurs at paclitaxel dose of 60mg/m^2, paclitaxel dosing should be maintained at 60mg/m^2 and ricolinostat reduced to the next lower dose level.		

Table 6.3.B: Dose modifications for thrombocytopenia		
	Hematologic Event	Dose Modification
Initial Occurrence	Grade 4 thrombocytopenia (platelets < 25,000/mcL) Grade 3 thrombocytopenia with bleeding event (platelets 25,000 to <50,000/mcL) Platelets < 100,000/mcL on Day 1 or <75,000/mcL on Day 8 or 15 Treatment delay > 7 days for thrombocytopenia	Reduce paclitaxel by one dose level
Second Occurrence	If any of the above toxicities occur after initial dose reduction	Reduce paclitaxel by one dose level Reduce ricolinostat by one dose level
Third occurrence	If any of the above toxicities occur after two dose reductions	Discontinue patient from protocol-directed therapy

6.4   Non-Hematologic Toxicities

6.4.1   Neuropathy

Neuropathy is a commonly observed toxicity with paclitaxel administration, and patients should be carefully monitored for development of neuropathy symptoms. Patients who develop grade 2 or higher neuropathy should be held until the neuropathy resolved to grade 1 or better. Study treatment may then be resumed with paclitaxel reduced by one dose level. Patients who are already on a dose of paclitaxel 60mg/m^2 weekly should be removed from protocol-directed therapy. Patients who do not have recovery of their neuropathy symptoms to grade 1 or better within 14 days should be removed from protocol-directed therapy.

For patients in the expansion cohort who have stable baseline grade 2 neuropathy, study treatment should be held for neuropathy that worsens to grade 3 or higher. Study treatment may be resumed at one dose level reduction of paclitaxel for patients whose neuropathy recovers to grade 2 within 14 days. If grade 3 or higher neuropathy recurs in these patients, protocol-directed therapy should be discontinued.

6.4.2   Hepatic Toxicity

Hepatic toxicity can be observed with paclitaxel administration. Liver function studies should be monitored during therapy as per protocol. Dose modifications for paclitaxel-related hepatic toxicity should be made as per the table below:

AST, ALT, and Alk Phos		Bilirubin	Paclitaxel Dosing
CTCAE grade 1	**AND**	≤ ULN	Continue current dose level
CTCAE grade 2	**OR**	CTCAE Grade 1	Reduce by one dose level[†].
≥ CTCAE grade 3	Or	≥ CTCAE Grade 2	Hold until recovered to AST, ALT, and alkaline phosphatase ≤ Grade 1 and bilirubin recovered to

			≤ ULN. Reduce by one dose level at time of treatment resumption
Second recurrence of any of the above after one dose reduction			Reduce paclitaxel by one dose level[††]
Recurrence of toxicity which would require a 3rd dose reduction			Discontinue protocol-directed therapy
[†]At the discretion of the investigator, treatment may be held until recovery of liver function tests to AST, ALT, and alkaline phosphatase ≤ Grade 1 and bilirubin ≤ ULN.			
[††]Paclitaxel dose may not be reduced below 60mg/m^2. If patient is at the lowest paclitaxel dose, protocol-directed therapy should be discontinued.			

6.4.3   Nausea

Nausea may be observed with both paclitaxel and ricolinostat. Nausea should be managed per institutional standards with supportive medications as needed. Dosing delays and reductions may be considered for patients with persistent grade 3 or higher nausea that is unresponsive to anti-emetic therapy. Dose reduction levels should be as outlined in Section 6.1. The investigator may choose to reduce the dose of paclitaxel, ricolinostat, or both, depending on which drugs are felt to be contributory to the development of nausea.

6.4.4   Diarrhea

Diarrhea may also be observed with both paclitaxel and ricolinostat and should be managed per institutional standards with supportive medications as needed. Dosing delays and reductions may be considered for patients with persistent grade 2 or higher diarrhea that remains uncontrolled despite maximal medical management. Dose reduction levels should be as outlined in Section 6.1. The investigator may choose to reduce the dose of paclitaxel, ricolinostat, or both, depending on which drugs are felt to be contributory to the development of diarrhea.

Recommended management for diarrhea is loperamide antidiarrheal therapy, with a dosage schedule of 4 mg at first onset, followed by 2 mg with each loose motion until diarrhea-free for 12 hours. The maximum dosage of loperamide should not exceed 16mg in a 24 hour period. Adjunct anti-diarrheal therapy is permitted and should be recorded when used.

6.4.5   Fatigue

Fatigue may be seen with paclitaxel and ricolinostat. Patients experiencing persistent grade 2 fatigue despite maximal support or grade 3 or higher fatigue may be dose-reduced as per the dose reduction levels outlined in Section 6.1 per investigator discretion. The investigator may choose to reduce the dose of paclitaxel, ricolinostat, or both.

6.5   Dose Modifications for Bevacizumab

In general, adverse events noted with bevacizumab should be managed by optimizing medical management, including with anti-hypertensives as required. Dose modifications for bevacizumab are not generally indicated for bevacizumab-related toxicities. Patients in the expansion cohort who experience a bevacizumab-related toxicity where it is felt that bevacizumab should be discontinued for safety considerations should be discussed with the study

PI.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

7.1 Expected Toxicities

7.1.1 Adverse Event List for Ricolinostat

Ricolinostat has been studied as monotherapy in a limited number of patients with multiple myeloma. Among patients treated with ricolinostat monotherapy, most AEs were reported to be Grade 1 or 2 in intensity and unrelated to study drug. Grade 3 AEs that were considered to be at least possibly related to ricolinostat were hematologic in nature, and included anemia, leucopenia, and neutropenia.

Additional non-hematologic AEs that have been observed in patients receiving ricolinostat monotherapy included blood creatinine increased (33%); fatigue (27%); hypercalcemia (27%); upper respiratory tract infection (27%); cough (20%); diarrhea (20%); and dizziness (20%). Of these events, diarrhea occurred at ricolinostat doses ≥ 160mg; no dose relationship was apparent with regard to the occurrence of any of the other AEs.

For additional information, please refer to the ricolinostat Investigator's Brochure.

7.1.2 Adverse Event List for Paclitaxel

Paclitaxel is FDA-approved for the treatment of ovarian cancer, and is associated with a number of toxicities, including nausea, vomiting, diarrhea, alopecia, constipation, peripheral neuropathy, myelosuppression, allergic/hypersensitivity reaction, bradycardia, nail changes, and elevation of liver function tests.

Please refer to the FDA package insert for a comprehensive list of adverse events.

7.1.3 Adverse Event List for Bevacizumab

Bevacizumab is FDA-approved in conjunction with paclitaxel, topotecan, or pegylated liposomal doxorubicin for the treatment of platinum-resistant ovarian cancer, and is associated with a number of toxicities, including hypertension, headache, epistaxis, hoarseness, proteinuria, thromboembolic events (venous and arterial), arthralgia, myalgia, infection, impaired healing, bleeding events, gastrointestinal perforation, fistula formation, myelosuppression, and allergic or infusion reactions.

Please refer to the FDA package insert for a comprehensive list of adverse events.

7.2   Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
  - Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3   Expedited Adverse Event Reporting

7.3.1   Investigators **must** report to the Overall PI any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

7.3.2   Cross-Reporting

All SAEs that occur during the course of the study must be reported to the Sponsor Investigator – Joyce Liu, MD, MPH at the contact information below. The Sponsor Investigator will notify INC Drug Safety (on behalf of Acetylon) within 1 business day, of all serious adverse events and expedited safety reports submitted to relevant regulatory authorities, as per the contact information below. All SAEs must be reported whether or not considered causally related to the study drug. SAE forms will be provided to each clinical study site. The information collected will include patient number, a narrative description of the event and an assessment by the Investigator as to the severity of the event and relatedness to study drug. Follow-up information on the SAE may be requested by Dana-Farber Cancer Institute and Acetylon.

Joyce Liu, M.D., MPH

joyce_liu@dfci.harvard.edu

INC Drug Safety on behalf of Acetylon - Drug Safety Reporting Contact Information

INC 1 business day SAE Reporting
E-mail: **incdrugsafety@incresearch.com**
Fax: 1 (877) 464-7787

If there are serious, unexpected adverse drug reactions associated with the use of the study drug, the Sponsor will notify the appropriate regulatory agency(ies) and all participating Investigators on an expedited basis. It is the responsibility of the Investigator to promptly notify the Institutional Review Board (IRB) of all unexpected serious adverse drug reactions involving risk to human patients. An unexpected event is one that is not reported in the Investigator's Brochure.

7.3.3   DF/HCC Expedited Reporting Guidelines

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

7.4   Expedited Reporting to the Food and Drug Administration (FDA)

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

7.5   Expedited Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.

7.6   Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must <u>also</u> be reported in routine study data submissions.**

8.   PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or other agents administered in this study can be found in Section 7.1.

8.1   Ricolinostat

8.1.1   **Description**
The International Nonproprietary Name (INN) and United States Adopted Name (USAN) of the active pharmaceutical ingredient (API) of ricolinostat Oral Solution is ricolinostat. Other codes used to identify the same compound during its development are ricolinostat, ACY-161-63 and ACY-63.

The International Union of Pure and Applied Chemistry (IUPAC) name of ricolinostat is 2-

(Diphenylamino)-N-(7-(hydroxyamino)-7-oxoheptyl)-pyrimidine-5-carboxamide.

Molecular Formula and Weight:
    Molecular Formula: $C_{24}H_{27}N_5O_3$
    Molecular Weight: 433.5

8.1.2 Study Drug

ACY-1215 Oral Solution, 10 mg/mL will be supplied by the Sponsor as a liquid for PO administration in amber glass bottles with a white child-resistant, tamper-evident cap. A total of 12 mL of the 10 mg/mL formulation is contained in each bottle of ACY-1215. ACY-1215 will be stored in the pharmacy at -20ºC. Additional storage conditions and dose preparation instructions will be provided in detail within the Pharmacy Manual.

Bottles will be supplied with a label attached to each bottle detailing product name and amount, lot number, date of manufacture, name of Sponsor, and the region-specific regulatory information.

Study drug labels will not contain any statement that is false or misleading in any manner or represent that the study drug is safe or effective for the purposes for which it is being investigated.

Dispensing of the amount needed for individual patients should be performed by appropriately trained personnel according to the pharmacy instructions.

8.1.3 Storage and Stability
ACY-1215 Oral Solution 10 mg/mL should be stored at -20°C at the clinical site. Patients should store ACY-1215 Oral Solution according to the instructions for use.

8.1.4 Compatibility
There are no known compatibility issues with oral ricolinostat and intravenous paclitaxel. During this phase Ib study, possible interactions will be monitored.

8.1.5 Handling
Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

8.1.6 Availability
Ricolinostat will be distributed by Acetylon Pharmaceuticals, Boston, MA.

8.1.7 Preparation
Dispensing of the amount needed for individual patients should be performed by appropriately trained personnel according to the pharmacy instructions in the pharmacy manual. Ricolinostat will come already prepared and no reconstitution will be necessary.

8.1.8 Administration
Patients should take ricolinostat every day at the same time (+/- 2 hours) at least 1 hour after ingestion of food and followed by 4 ounces of water. Patients should not ingest food or other PO

medication for at least 2 hours after each dose of ricolinostat.

8.1.9 Ordering
ACY-1215 Oral Solution, 10 mg/mL will be ordered by the research pharmacy through Acetylon Pharmaceuticals, Boston, MA, using the process described in the Pharmacy Manual.

8.1.10 Accountability
The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

8.1.11 Destruction and Return
Destruction of unused ACY-1215 Oral Solution, 10 mg/mL will be as per institutional research pharmacy policies.

8.2 Paclitaxel

8.2.1 Description
Paclitaxel is a chemotherapy agent that disrupts microtubule formation and is commonly used in many cancers for treatment.

8.2.2 Form
Paclitaxel is supplied as a 6mg/mL non-aqueous solution in multi dose vials containing 30mg/5mL, 100mg/16.7mL, or 300mg/50mL of paclitaxel. In addition to 6mg of paclitaxel, each mL of sterile non-pyrogenic solution contains 527mg of purified Cremophor® EL (polyoxyethylated castor oil) and 49.7% (v/v) dehydrated alcohol, USP.

8.2.3 Storage and Stability
Unopened vials of paclitaxel are stable to the date indicated on the package when stored between 20 to 25°C (68 to 77°F). Protect from light.

Commercially available paclitaxel will be labeled with an expiration date. All solutions of paclitaxel exhibit a slight haziness directly proportional to the concentration of drug and the time elapsed after preparation, although when prepared as described below, solutions of paclitaxel (0.3-1.2mg/ml) are physically and chemically stable for 27 hours.

8.2.4 Compatibility
There are no known compatibility issues with oral ricolinostat and intravenous paclitaxel.

8.2.5 Handling
Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

8.2.6 Availability
Paclitaxel is commercially available both from Bristol-Myers Squibb Oncology as well as generic manufacturers. Consult the American Hospital Formulary Service Drug Information

guide, Facts and Comparisons, or the package insert for additional information.

8.2.7 Preparation

Paclitaxel must be diluted prior to infusion. Paclitaxel should be diluted in 0.9% Sodium Chloride for Injection, USP; 5% Dextrose Injection, USP; 5% Dextrose and 0.9% Sodium Chloride Injection, USP; or 5% Dextrose in Ringer's Injection to a final concentration of 0.3 to 1.2mg/mL. The solutions are physically and chemically stable for up to 27 hours at ambient temperature (approximately 25°C / 77°F) and room lighting conditions.

NOTE: In order to minimize patient exposure to the plasticizer DEHP, which may be leached from PVC infusion bags or sets, diluted paclitaxel solutions should be stored in bottles (glass, polypropylene) or plastic (polypropylene, polyolefin) bags and administered through polyethylene-lined administration sets.

8.2.8 Administration

Paclitaxel should be administered through an inline filter with a microporous membrane not greater than 0.22 microns. Use of filter devices such as IVEX-2® or IVEX-HP®, which incorporate short inlet and outlet PVC-coated tubing, has not resulted in significant leaching of DEHP.

Weekly dosing of paclitaxel should be given via intravenous infusion over a period of approximately 60 minutes.

All patients should be premedicated with corticosteroids, diphenhydramine, and H2 antagonists prior to paclitaxel administration in order to prevent severe hypersensitivity reactions as dictated by national treatment guidelines, FDA package insert recommendations, and individual hospital policies and procedures. Patients who experience severe hypersensitivity reactions to drug may need to repeat the premedication and to be re-challenged with a dilute solution and slow infusion. Severe life-threatening hypersensitivity reactions to paclitaxel should not proceed with a re-challenge, and consultation of an allergy specialist should be obtained if any type of allergic reaction occurs with paclitaxel for future guidance on management.

8.2.9 Ordering

Paclitaxel is commercially available and will be ordered by the institution's pharmacy.

8.2.10 Accountability

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form.

8.2.11 Destruction and Return

Unused paclitaxel will be destroyed as per individual institutional pharmacy policies and procedures.

8.3   Bevacizumab

8.3.1 Description

Bevacizumab is a recombinant humanized anti-VEGF monoclonal antibody. Bevacizumab

blocks the binding of vascular endothelial growth factor (VEGF) to its receptors resulting in inhibition of angiogenesis.

8.3.2 Form
Bevacizumab is supplied as a clear to slightly opalescent, sterile liquid ready for parenteral administration. Each 400mg or 100mg glass vial contains bevacizumab with phosphate, trehalose, polysorbate 20, and Sterile Water for Injection, USP.

8.3.3 Storage and Stability
Bevacizumab should be stored in the refrigerator (2° to 8°C) and should remain refrigerated until just prior to use. Do not freeze. Do not shake. Commercially available bevacizumab will be labeled with an expiration date.

8.3.4 Compatibility
There are no known compatibility issues with oral ricolinostat and intravenous bevacizumab.

8.3.5 Handling
Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

8.3.6 Availability
Bevacizumab is commercially available from Genentech, Inc. Consult the American Hospital Formulary Service Drug Information guide, Facts and Comparisons, or the package insert for additional information.

8.3.7 Preparation
Vials contain no preservative and are intended for single use only. Place the calculated dose in 100mL of 0.9% sodium chloride for injection.

8.3.8 Administration
Bevacizumab is administered intravenously as a continuous infusion. The initial dose should be administered over a minimum of 90 minutes (+/- 10 min). If no adverse reactions occur after the initial dose, the second dose should be administered over a minimum of 60 minutes (+/0 10 min). If no adverse reactions occur after the second dose, all subsequent doses should be administered over a minimum of 30 minutes (+/- 10 min). If infusion-related adverse reactions occur, all subsequent infusions should be administered over the shortest period that was well-tolerated.

8.3.9 Ordering
Bevacizumab is commercially available and will be ordered by the institution's pharmacy.

8.3.10 Accountability
The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form.

8.3.11 **Destruction and Return**

Unused bevacizumab will be destroyed as per individual institutional pharmacy policies and procedures.

9. SPECIAL STUDIES: NEUROLOGICAL ASSESSMENT

Paclitaxel is associated with the development of chemotherapy-induced neuropathy. Based upon pre-clinical data, it is hypothesized that ricolinostat may prevent development or worsening of chemotherapy-induced neuropathy in patients receiving weekly paclitaxel therapy. Patients in the dose expansion cohorts will therefore undergo additional neurologic evaluation as detailed below to assess on-treatment changes in neuropathy signs and/or symptoms.

9.1   Total Neuropathy Score-Nurse (TNSn©)

9.1.1   Background

Paclitaxel is an active agent in a variety of solid tumors through its inhibition of microtubule dynamics leading to aberrant mitosis and cell death. Its activity on microtubules is also thought to be associated with one of the most debilitating side effects of this class of drugs, chemotherapy-induced peripheral neuropathy (CIPN). In animal models paclitaxel has been found in the dorsal root ganglia of the peripheral nervous system (26) and leads to demyelination and disrupted axoplasmic transport (27). This results in pain and decreased sensitivity, particularly in body parts with long nerve tracts, such as the extremities. In patients paclitaxel-induced peripheral neuropathy varies with dose and schedule from 46 to 79% for any CIPN and 2 to 28% of patients have > grade 3 CIPN (paclitaxel label). CIPN frequently leads to paclitaxel dose reductions and at times to treatment discontinuation. Currently there is no FDA-approved drug available for treatment of CIPN.

This study will implement the TNS© to assess baseline peripheral neuropathy and intermittently during the course of treatment in the expansion phase of the trial. The TNSn© will be used to evaluate peripheral nerve function and changes in it that might occur during the clinical trial. TNSn© was designed specifically to be implemented by trained health professionals who are not necessarily neurologists. TNSn© is based on the Total Neuropathy Score© (TNS©) which was validated in diabetic neuropathy (28). TNS© and its spin-offs such as TNSc©(clinical) and TNSn© have been widely used in single center academic studies, multi-center academic studies and multi-center clinical trials.

The TNSn© focuses on the detection of and change in the onset and progression of peripheral neuropathy by measuring five categories: sensory, motor, and autonomic symptoms, sensibility to "pin" (small fiber sensory function) and sensibility to vibration (large fiber function). Key features include bilateral assessment of function, measurements along a distal-to-proximal gradient and the use of established and quantitative measures of sensation. The output of the TNSn© is a total score on a 0-20 scale, with five distinct sub-scores each on a 0-4 scale.

 Further details are in Appendix B.

9.1.2   Method of Assessment

The TNSn© will be assessed by the research nursing team. The full TNSn© assessment is included in Appendix B. Research nurses will be trained on use of the TNSn© prior to administration to any patients.

9.1.3   Timing of Assessments

The TNSn© will be administered only to patients in the expansion cohort at baseline, on day 1 of cycles 1, 2, and 3, and on day 1 of every other cycle thereafter. The TNSn© will also be administered at the end of treatment visit. If the TNSn© cannot be administered on day 1 of a given cycle, it may be "made up" at the next subsequent visit.

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 1 week prior to start of protocol therapy. Scans and x-rays must be done ≤4 weeks prior to the start of therapy. In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

Assessments must be performed prior to administration of any study agent. Study assessments and agents should be administered within ± 3 days of the protocol-specified date, unless otherwise noted.

All study assessments and agents during the DLT assessment period must be administered on the protocol-specified date; no treatment windows are allowed during the DLT assessment period with the exception of those mandated by holidays, in discussion with the overall PI.

	Pre-Therapy	Each Cycle Day 1,8,15	Each Cycle Day 1 only	Every other cycle	Off of all study therapy
Informed Consent	1				
Medical History	1				
Physical Examination	1	X			X
Vital signs (Blood Pressure, Heart Rate and Temperature)	1	X			X
Performance Status (ECOG)	1	X			X
Adverse Event Assessment	2	X			3
CBC/Differential/Platelets	2	X			X

PT/INR and PTT	2				X
Serum chemistry[4]	2	X			X
Urinalysis	2	X[5]			
Pregnancy Test (if childbearing potential exists)	2				
Radiographic tumor measurement	1			6	
CA-125	2		X		
Electrocardiogram (ECG)	1		X		
Neurological testing	7			8	X
Patient Medication Calendar for ricolinostat recording		9			

One cycle = 28 days

Notes:
1. Must be obtained within 28 days prior to initiating protocol therapy.
2. Must be obtained within 14 days prior to initiating protocol therapy.
3. Report all adverse events that occur within 30 days of last protocol treatment.
4. Serum chemistry includes the following: sodium, potassium, chloride, bicarbonate, BUN, creatinine, gluocose, calcium, magnesium, AST (SGOT), ALT (SGPT), alkaline phosphatase, total bilirubin, total protein, albumin, globulin
5. Required at baseline for all patients. Required at days 1 and 15 of each cycle only for patients in Expansion Cohort C.
6. Tumor measurements by CT scan or MRI should be performed every 2 cycles (+/- 7 days) and include imaging of the chest, abdomen, and pelvis. The same modality should be used throughout the study unless contraindicated for medical reasons.
7. As detailed in Section 9.1
8. Should be performed on Day 1 of Cycle 1, 2, 3, and then every other cycle, as detailed in Section 9.1. If performed as baseline testing within 7 days of Cycle 1 Day 1, the TSRn does not need to be repeated for Cycle 1 Day 1.
9. Patients should record ricolinostat dosing in the medication diary as per Appendix C.

11. MEASUREMENT OF EFFECT

Although response is not the primary endpoint of this trial, participants with measurable disease will be assessed by standard criteria. For the purposes of this study, participants should be re-evaluated every 2 cycles. In addition to a baseline scan, confirmatory scans will also be obtained at least 4 weeks following initial documentation of an objective response; the next planned restaging imaging study may be used as the confirmatory scan.

11.1   Antitumor Effect – Solid Tumors

For the purposes of this study, participants should be re-evaluated for response every 2 cycles.

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Definitions

Evaluable for Target Disease response. Only those participants who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for target disease response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Participants who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as $\geq$ 20 mm by chest x-ray or $\geq$10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area should not be considered measurable unless they have demonstrated progression following radiation.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be $\geq$15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all considered non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same participant, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow up.

11.1.3 Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation using a ruler, calipers, or a digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

<u>Clinical lesions.</u> Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm in diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

<u>Chest x-ray.</u> Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung; however, CT is preferable.

<u>Conventional CT and MRI.</u> This guideline has defined measurability of lesions on CT scan based on the assumption that CT thickness is 5mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size of a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

<u>FDG-PET.</u> While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
    (a) Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
    (b) No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
    (c) FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

PET-CT. At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later data and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is necessary to document progression. If there is concern about radiation exposure from CT, MRI may be used instead of CT in selected instances.

Tumor markers. Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a participant to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

11.1.4 Response Criteria

11.1.4.1   Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

11.1.4.2   Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

11.1.4.3   Evaluation of New Lesions

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

11.1.4.4   Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Participants with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

*   See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
**   Only for non-randomized trials with response as primary endpoint.
***   In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

For Participants with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

*   'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

11.1.5 <u>Duration of Response</u>

<u>Duration of overall response</u>: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started, or death due to any cause. Participants without events reported are censored at the last disease evaluation).

<u>Duration of overall complete response</u>: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

<u>Duration of stable disease</u>: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

11.1.6 <u>Progression-Free Survival</u>

<u>Overall Survival</u>: Overall Survival (OS) is defined as the time from randomization (or registration) to death due to any cause, or censored at date last known alive.

<u>Progression-Free Survival</u>: Progression-Free Survival (PFS) is defined as the time from randomization (or registration) to the earlier of progression or death due to any cause. Participants alive without disease progression are censored at date of last disease evaluation.

<u>Time to Progression</u>: Time to Progression (TTP) is defined as the time from randomization (or registration) to progression, or censored at date of last disease evaluation for those without progression reported.

11.1.7 <u>Response Review</u>

Scans will be evaluated by the Dana Farber/Harvard Cancer Center Tumor Imaging Metrics Core (DF/HCC TIMC).

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1   Data Reporting

12.1.1 <u>Method</u>

The ODQ will collect, manage, and perform quality checks on the data for this study.

12.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the ODQ according to the schedule set by the ODQ.

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring with 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Collaborative Agreements Language

N/A. Ricolinostat (ACY-1215) will be provided as an investigational product by Acetylon Pharmaceuticals, Inc.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

This is a phase Ib study, and the primary objective is to determine the MTD dose of ricolinostat with weekly paclitaxel dosed at 80 mg/m2 per week (3 out of 4 weeks). The study design is a 3+3 design, escalating if 0/3 or 1/6 participants have a DLT during the first cycle of therapy (i.e. the first 28 days), at the discretion of the Principal Investigator. If additional experience is necessary with a dose level that has passed the DLT period, 3 additional patients may be entered at the discretion of the principal investigator and also at the suggestion of Acetylon.

The planned dose escalation and dose levels of ricolinostat for this study are outlined in Section 5.1. If treatment-related toxicities emerge during the course of this study, additional interim dose levels may be added based upon the observed toxicities.

Probabilities of dose escalation (based on a binomial distribution) are tabulated below for a series of assumed true toxicity rates:

True	0.1	0.2	0.3	0.4	0.5	0.6	0.65	0.7	0.8	0.9

Toxicity Rate										
Probability of Escalation	0.91	0.71	0.49	0.31	0.17	0.08	0.053	0.032	0.009	0.001

At least 6 patients will be treated at MTD, and no more than 1 patient should experience a DLT at the MTD level. Based on the exact binomial distribution, we would be unlikely to escalate the dose (the probability is 0.053) if the true toxicity was 65% or greater.

Once the MTD/RP2D of ricolinostat with paclitaxel has been established, an additional 10 patients will be added who have no significant peripheral neuropathy (grade 1 or less) at the MTD (Expansion cohort A) as well as 10 patients who have grade 2 peripheral neuropathy at the MTD dose of ricolinostat together with paclitaxel at 70mg/m2 per week (3 out of 4 weeks) (Expansion cohort B).

An additional cohort at the MTD (Expansion cohort C) will also be enrolled to evaluate the addition of bevacizumab to the RP2D of ricolinostat with paclitaxel. To ensure patient safety, this cohort will enroll 3 patients; if no DLT events are observed, an additional 3 patients will be enrolled, and if no or 1 DLT are observed in the 6 patients, an additional 4 patients will be enrolled.

13.2   Sample Size, Accrual Rate and Study Duration

Depending on the number of dose levels, it is anticipated that between 15 and 24 patients will be enrolled to the dose escalation portion of this study and up to 30 patients will be enrolled to the three expansion cohorts with 10 patients each. With 10 patients in each cohort, the probability of observing at least one serious toxicity event is 80% if the true toxicity rate is 15%. With 10 participants, the maximum width to a binomial exact 90% confidence interval is 0.56.

Accrual rate will be up to 3 patients per month because of the phase I dose escalation design. Once the MTD has been reached, and the dose expansion cohorts are opened, accrual will be 2 to 4 patients per month. Therefore, the anticipated total accrual duration will be between 13 to 23 months.

13.3   Stratification Factors

Once the MTD of the phase Ib has been determined, expansion cohorts will be enrolled with patients with no clinically significant neuropathy at the start of treatment (CTCAE grade 0 or 1; Cohorts A and C) and patients with grade 2 neuropathy (Cohort B). Up to 10 patients will be treated in both cohorts.

13.4   Interim Monitoring Plan

There is no interim monitoring plan in this study.

13.5   Analysis of Primary Endpoints

The initial analysis will report on the MTD in the dose escalation portion of the study, including toxicity profile. All participants will be evaluable for toxicity if they received any protocol therapy. All assessments will be performed by dose level. All participants will be analyzed in their dose assigned group, even with intra-patient dose escalation.

13.6   Analysis of Secondary Endpoints

The following secondary endpoints will be explored in the expansion cohorts:

(1) Toxicities especially peripheral neurotoxicity assessed using TNS© by measuring five categories: sensory, motor, and autonomic symptoms, sensibility to "pin" (small fiber sensory function) and sensibility to vibration (large fiber function). The output of the TNSn© is a total score on a 0-20 scale, with five distinct sub-scores each on a 0-4 scale (Section 9).

(2) Best Overall Response, defined as the best response recorded from the start of the treatment until disease progression/recurrence (Section 10.1.3.4).

(3) Duration of overall response (DOR), measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented. Participants without events reported are censored at the last disease evaluation (Section 10.1.4),

(4) Progression-free survival (PFS), defined as the duration of time from registration to progression, or death due to any cause, whichever occurs first. Participants alive without disease progression are censored at date of last disease evaluation (Section 10.1.5).

The limited number of subjects will provide insufficient statistical power for a formal cohort analysis and statistical inferences. However, we will explore trends across groups as a descriptive analysis plan that is estimation-only.

The TNSn© is a straightforward tool to evaluate baseline peripheral neuropathy and its development throughout the treatment course. The TNSn© focuses on the detection of and change in the onset and progression of peripheral neuropathy by measuring five categories: sensory, motor, and autonomic symptoms, sensibility to "pin" (small fiber sensory function) and sensibility to vibration (large fiber function). Key features include bilateral assessment of function, measurements along a distal-to-proximal gradient and the use of established and quantitative measures of sensation. The output of the TNSn© is a total score on a 0-20 scale, with five distinct sub-scores each on a 0-4 scale. Further details are in Appendix B or the Manual of Operations. Descriptive statistics for the semi-quantitative neurotoxicity scale (e.g., quantiles, ranges, means, SD) will be computed for baseline assessments and for absolute change from baseline at each specified follow-up visit (e.g, completion of the 4th week cycle) within each cohort. Graphic methods (e.g., box plots and histograms) will also be employed to closely examine distributions of the longitudinal measures. The same descriptive analysis will be performed for each sub-component of the TNSn.

All participants will be evaluable for toxicity if they received any protocol therapy. All participants who have received at least one dose of protocol therapy will be included in the

efficacy analysis. All assessments will be performed by dose level. All participants will be analyzed in their dose assigned group, even with intra-patient dose escalation.

The frequency of all binary and categorical endpoints of safety and efficacy will be reported using 95% binomial exact confidence intervals. Time-to-event analysis of DOR and PFS will be based on the Kaplan-Meier product-limit estimator, using 95% confidence interval.

SAS computer software 9.4 will be used for this analysis.

13.7   Reporting and Exclusions

13.7.1 Evaluation of Toxicity

All participants will be evaluable for toxicity from the time of their first treatment.

13.7.2 Evaluation of the Primary Efficacy Endpoint

Analyses will be performed employing intent-to-treat. Specifically, all participants included in the study must be assessed for response/outcome to therapy, even if there are major protocol therapy deviations or if they are ineligible. Each participant should be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.

14. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

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APPENDIX A   PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B   TOTAL NEUROPATHY SCORE-NURSE (TNSn©)

Total Neuropathy Score-Nurse (TNSn)
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TNSn Worksheet Overall Scores

Center No: _____   Subject No: _____   Subject Initials: _____

Visit Number: _____   Visit Date: _____

_____   _____
Name of Person Evaluating TNSn   Signature of Person Evaluating TNSn

Sensory Symptom Score (0-4):   _____

Motor Symptom Score (0-4):   _____

Autonomic Symptom Score (0-4):   _____

Pin Sensibility Score (0-4):   _____

Vibration Sensibility Score (0-4):   _____

TNSn Total (0-20): _____

TNSn Worksheet: 1. Sensory Symptoms

| Center No: _____ | Subject No: _____ | Subject Initials: _____ |
| Visit Number: _____ | Visit Date: _____ | page 2 of 6 |

Instructions: Ask the subject whether he/she has had the following symptoms on multiple occasions or for a sustained period over the past week which can not be attributed to other causes (for instance, osteoarthritis pain). Check the box that applies to the level of the symptom for the site (e.g., either finger or toe) and the side outlined.

Paresthesias (tingling) in Lower Limbs:

	Right	Left	Score
None	☐	☐	0
Limited to toes	☐	☐	1
Above toes to ankle	☐	☐	2
Above ankle to knee	☐	☐	3
Above knee	☐	☐	4

Highest Score of either side (0-4): _____

Paresthesias (tingling) in Upper Limbs:

	Right	Left	Score
None	☐	☐	0
Limited to fingers	☐	☐	1
Above fingers to wrist	☐	☐	2
Above wrist to elbow	☐	☐	3
Above elbow	☐	☐	4

Highest Score of either side (0-4): _____

Numbness in Lower Limbs (dead asleep):

	Right	Left	Score
None	☐	☐	0
Limited to toes	☐	☐	1
Above toes to ankle	☐	☐	2
Above ankle to knee	☐	☐	3
Above knee	☐	☐	4

Highest Score of either side (0-4): _____

Numbness in Upper Limbs (dead asleep):

	Right	Left	Score
None	☐	☐	0
Limited to fingers	☐	☐	1
Above fingers to wrist	☐	☐	2
Above wrist to elbow	☐	☐	3
Above elbow	☐	☐	4

Highest Score of either side (0-4): _____

Neuropathic pain in Lower Limbs (burning, aching, stabbing):

	Right	Left	Score
None	☐	☐	0
Limited to toes	☐	☐	1
Above toes to ankle	☐	☐	2
Above ankle to knee	☐	☐	3
Above knee	☐	☐	4

Highest Score of either side (0-4): _____

Neuropathic pain in Upper Limbs (burning, aching, stabbing):

	Right	Left	Score
None	☐	☐	0
Limited to fingers	☐	☐	1
Above fingers to wrist	☐	☐	2
Above wrist to elbow	☐	☐	3
Above elbow	☐	☐	4

Highest Score of either side (0-4): _____

Sensory Symptom Score (0-4): _____
Enter the highest of the 6 scores

TNSn Worksheet: 2. Motor Symptoms

Center No: _____   Subject No: _____   Subject Initials: _____

Visit Number: _____   Visit Date: _____   page 3 of 6

Instructions: Ask the subject whether he/she has had any of the following deficits on multiple occasions or for a sustained period over the past week which can not be attributed to other causes (for instance, osteoarthritis pain). Score motor symptoms on the right and left sides separately.

FEET - (e.g., difficulty walking on tip toes or heels, difficulty clearing foot over a curb or step, or operating pedals in a car)

	Right	Left	Score
No Difficulty	☐	☐	0
Slight Difficulty	☐	☐	1
Moderate Difficulty	☐	☐	2
Requires help/assistance device	☐	☐	3
Total Loss of Function	☐	☐	4

Highest Score of either side (0-4): _____

LEGS - (e.g., difficulty climbing steps or standing from a sitting position)

	Right	Left	Score
No Difficulty	☐	☐	0
Slight Difficulty	☐	☐	1
Moderate Difficulty	☐	☐	2
Requires help/assistance device	☐	☐	3
Total Loss of Function	☐	☐	4

Highest Score of either side (0-4): _____

HANDS - (e.g., difficulty with buttoning, writing, tying shoelaces, opening tight jars or inserting key in lock)

	Right	Left	Score
No Difficulty	☐	☐	0
Slight Difficulty	☐	☐	1
Moderate Difficulty	☐	☐	2
Requires help/assistance device	☐	☐	3
Total Loss of Function	☐	☐	4

Highest Score of either side (0-4): _____

ARMS - (e.g., difficulty combing hair, using a hair dryer or reaching to high shelf)

	Right	Left	Score
No Difficulty	☐	☐	0
Slight Difficulty	☐	☐	1
Moderate Difficulty	☐	☐	2
Requires help/assistance device	☐	☐	3
Total Loss of Function	☐	☐	4

Highest Score of either side (0-4): _____

Motor Symptom Score (0-4): _____
Enter the highest of the 4 scores

TNSn Worksheet: 3. Autonomic Symptoms

Center No: _____	Subject No: _____	Subject Initials: _____
Visit Number: _____	Visit Date: _____	page 4 of 6

Instructions: Ask the subject if any of the following conditions has occurred on multiple occasions or for a sustained period over the past week which can not be attributed to other causes (for instance, flu). Check "Yes" or "No" for each:

	Yes	No
1. Lightheadedness or dizziness when getting up from a lying position	☐	☐
2. Difficulty eating a meal because you get full too quickly or get bloated	☐	☐
3. Diarrhea that wakes you at night	☐	☐
4. Constipation	☐	☐
5. Problems controlling your bladder	☐	☐
6. Difficulty with erections (men only) ☐ N/A	☐	☐

Number of "Yes" Answers (0-6): _____

Autonomic Symptom Score (0-4): _____

0 = no symptoms
1 = 1 symptom
2 = 2 symptoms
3 = 3 symptoms
4 = 4 or more symptoms

TNSn Worksheet: 4. Pin Sensibility

Center No: _____   Subject No: _____   Subject Initials: _____

Visit Number: _____   Visit Date: _____   page 5 of 6

Instructions: Prior to testing, please gain familiarity with the Neuropen device (see Manual). The Neuropen has a "sharp" Neurotip pin on one end and a "dull" 10g monofilament on the other end. Begin testing at the finger/toe. During testing, you will contact the subject at a specified site with one of the stimuli and ask, "does this feel sharp or dull?" Present 10 stimuli, with a random order of 5 "sharp" and 5 "dull" stimuli. Hold the Neuropen approximately perpendicular to the site of stimulation and continue to press until the pressure gauge reaches the 40g marker zone for the "sharp" pin stimulus, or until the "dull" monofilament bends to form a "C." Hold each stimulus for 1-2 seconds. If the subject correctly identifies 8 or more of the 10 stimuli at the finger/toe, enter a check in the Normal box for that site and stop testing that limb. If the subject makes more than 2 errors in the 10 presentations, check the Abnormal box and test the next most proximal location.

Locations: great toe: top surface of the great toe immediately proximal to the nail bed
　　　　　ankle: top surface of the ankle midway between the lateral and medial malleolus
　　　　　knee: overlying the medial epicondyle of the femur
　　　　　mid-thigh: anterior surface of quadriceps muscle midway between the knee and hip

　　　　　finger: top surface of the index finger immediately proximal to the nail bed
　　　　　wrist: top surface of the wrist, at the midline approximately 1 cm proximal to the wrist crease
　　　　　elbow: overlying the medial epicondyle
　　　　　mid-upper arm: anterior surface over biceps muscle

Lower Limbs	**Right** ☐ not all sites accessible		**Left** ☐ not all sites accessible	
	Normal	Abnormal	Normal	Abnormal
Great Toe	☐	☐	☐	☐
Ankle	☐	☐	☐	☐
Knee	☐	☐	☐	☐
Thigh	☐	☐	☐	☐
	Score: _____		Score: _____	

Upper Limbs	**Right** ☐ not all sites accessible		**Left** ☐ not all sites accessible	
	Normal	Abnormal	Normal	Abnormal
Finger	☐	☐	☐	☐
Wrist	☐	☐	☐	☐
Elbow	☐	☐	☐	☐
Upper Arm	☐	☐	☐	☐
	Score: _____		Score: _____	

Score As:
0 = normal at finger/toe
1 = abnormal at finger/toe, but normal at wrist/ankle
2 = abnormal at wrist/ankle, but normal at elbow/knee
3 = abnormal at elbow/knee, but normal above the
　　elbow/knee
4 = abnormal above the elbow/knee

Pin Sensibility Score (0-4): _____
Enter the highest of the 4 scores

TNSn Worksheet: 5. Vibration Sensibility

Center No: _____	Subject No: _____	Subject Initials: _____
Visit Number: _____	Visit Date: _____	Age: _____ page 6 of 6

Instructions: Prior to testing, please gain familiarity with the Rydel Seiffer graduated tuning fork (see Manual). Begin by strongly pinching the top of the tuning fork using two fingers. Never bang the tuning fork against a hard object. Place the metal bulb at the base of the stem of the tuning fork against the skin at the test site and hold the fork with moderate pressure approximately perpendicular to the test surface. Throughout testing, maintain an unobstructed view of the triangle on each prong. As the vibration intensity diminishes, an optical illusion will cause the appearance of two merging triangles on each prong, with the point of their intersection gradually ascending. Note the vibration intensity on the 0-8 scale at the time the subject reports that he/she can no longer feel the vibration and enter the intensity to the nearest 0.5 units. If the subject reports that he/she does not feel the vibration at the initial contact, enter a score of 0.

When (if) a "Normal" Vibration Score is obtained, stop testing that limb/side.

Locations: Great Toe: top surface of great toe immediately proximal to the nail bed
Ankle: top surface of the medial malleolus
Knee: overlying the medial epicondyle of the femur
Hip: overlying the iliac crest

Finger: top surface of index finger immediately proximal to the nail bed
Wrist: surface of the ulnar styloid
Elbow: overlying the medial epicondyle
Shoulder: overlying the acromion

Lower Limbs — Right / Left, Vibration Score, Normal/Abnormal: Great Toe, Ankle, Knee, Hip. Score: ____

Upper Limbs — Right / Left, Vibration Score, Normal/Abnormal: Finger, Wrist, Elbow, Shoulder. Score: ____

Lower Limb Vibration Reference Values
Age (years)	Values
< or = 40	> or = 4.5
41-60	> or = 4.0
61-85	> or = 3.5
>85	> or = 3.0

Upper Limb Vibration Reference Values
| Age (years)	Values
< or = 40	> or = 6.5
41-85	> or = 6.0
>85	> or = 5.5

Sensibility Scoring
0 = normal for age at the finger/toe
1 = abnormal for age at finger/toe, but normal at wrist/ankle
2 = abnormal for age at wrist/ankle, but normal at elbow/knee
3 = abnormal for age at elbow/knee, but normal above the elbow/knee
4 = abnormal for age above the elbow/knee

Vibration Sensibility Score (0-4): _____
Enter the highest of the 4 scores

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Total Neuropathy Score – nurse (TNSn)

The Rydel Seiffer Graduated Tuning Fork
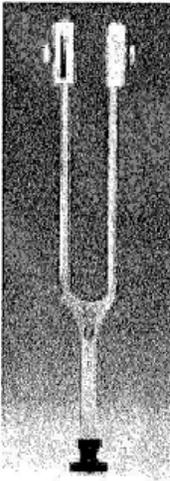
The tuning fork produces two different frequencies: note C – 64 Hz with the dampers (as marked on the dampers) and note C = 128 Hz without the dampers. The dampers must be fitted with the lower edge flush with the gradations on the prongs. The imprint "C64" on the dampers, and the imprint "C128" on the front of the tuning fork must all be facing the user when the dampers are fitted. The knurled head screws are tightened to fix the dampers and slacked to remove them. They should be tightened firmly when the dampers are fitted.

Practical use

Notice the black and white triangles on the dampers, each with a scale from 0 to 8. When the tuning fork is struck against the ball of the thumb (never strike it against a hard surface), the prongs start to oscillate and the illusion of two triangles is visible on each damper. The base of the tuning fork is placed over the appropriate bony surface (ie distal hallux, medial malleolus etc) and the patient is asked to indicate the moment when the vibration is not longer
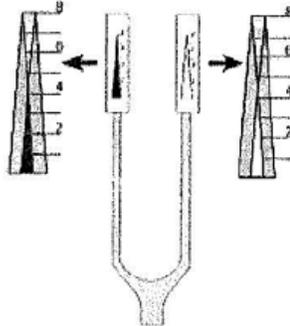
detected. As the intensity of the vibration starts to diminish the two triangles move closer together again and their point of intersection moves slowly upward. The intensity at which the patient no longer detects the vibration is read as the number adjacent the intersection of the vibrating damper triangles. This number can be read off the white or black triangle depending on the amount of light available or which scale is more easily readable. Recording the black triangle intersection from the bottom up and the white triangle intersection from the top down produces the most accurate readings between triangles for any particular moment in time.

Reference values for normal healthy controls have been published in the Journal of Neurology, Neurosurgery and Psychiatry 1998;65(5)743-7.

Upper Extremities		Lower Extremities	
Age	Values	Age	Values
≤ 40	≥ 6.5	≤ 40	≥ 4.5
41-85	≥ 6.0	41-60	≥ 4.0
>85	≥ 5.5	61-85	≥ 3.5
		>85	>3.0

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APPENDIX C: PATIENT DRUG DIARY (DOSE LEVELS 1 THROUGH 4)

Today's Date _____ Cycle # _____

Patient Name _____ Patient Study ID _____

1. Complete one form for each cycle (28 days).
2. Record the date, the dose you took, and when you took it.
3. Take dose 1 hour after eating followed by a half glass of water; do not eat for 2 hours after taking dose.
4. If you miss a dose, you have up to 2 hours to make this dose up. Otherwise, write "missed" where you would normally write the time of your dose. Do not make up vomited doses.
5. Refrain from taking herbal medications, eating citrus fruits and drinking citrus juices.
6. Blacked out rows are days where you would not be expected to take ricolinostat.
7. The first row in the table below is an EXAMPLE ROW for how to complete this diary.

RICOLINOSTAT

Take _____ (number) _____ mg once daily at least 1 hour after and 2 hours before any food or other medications.

Day	Date	Milligrams taken	Time	Please note if dose not taken here
1	*1/1/15*	*80*	*8:00 AM*	*--*
1				
2				
3				
4				
5				
6				
7				
8				
9				
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26				
27				
28				

Patient's Signature: _____ Date: _____

Physician/Nurse/Data Manager's Signature _____ Date_____

APPENDIX D: PATIENT DRUG DIARY (DOSE LEVEL -1 ONLY)

Today's Date _____   Cycle # _____

Patient Name _____   Patient Study ID _____

1. Complete one form for each cycle (28 days).	
2. Record the date, the dose you took, and when you took it.	
3. Take dose 1 hour after eating followed by a half glass of water; do not eat for 2 hours after taking dose.	
4. If you miss a dose, you have up to 2 hours to make this dose up. Otherwise, write "missed" where you would normally write the time of your dose. Do not make up vomited doses.	
8. Refrain from taking herbal medications, eating citrus fruits and drinking citrus juices.	
5. Blacked out rows are days where you would not be expected to take ricolinostat.	
6. The first row in the table below is an EXAMPLE ROW for how to complete this diary.	

RICOLINOSTAT

Take _____ (number) _____ mg once daily at least 1 hour after and 2 hours before any food or other medications.

Day	Date	Milligrams taken	Time	Please note if dose not taken here
1	*1/1/15*	*80*	*8:00 AM*	*--*
1				
2				
3				
4				
5				
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Patient's Signature: _____   Date: _____

Physician/Nurse/Data Manager's Signature _____   Date_____